

AMENDMENTS TO THE CLAIMS

1. (currently amended) A method of preparing the chiral (\pm) isomers of indole-2,3-dione-3-oxime derivatives (~~Compounds A or B~~), which method comprises the subsequent sequential steps of:

(i) reacting an 8-amino-1,2,3,4-tetrahydro-isoquinoline (~~Compound 9~~) derivative with chloral hydrate and hydroxylamine hydrochloride to give an *N*-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-2-hydroxyimino-acetamide (~~Compound 10~~) derivative (Step 9);

(ii) adding sulphuric acid to the *N*-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-2-hydroxyimino-acetamide (~~Compound 10~~) derivative obtained in step (i) to provide a 2,3-dioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline (Step 10); and

(iii) reacting the 2,3-dioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline (~~Compound 11~~) derivative obtained in step (ii) with chiral (enantiopure (*R*) or (*S*)) α -*N,N*-diBoc-aminoxy- γ -butyrolactone to obtain the desired chiral end product, i.e. enantiopure (*R*)- or (*S*)-2-[2-oxo-1,2,6,7,8,9-hexahydro-pyrrolo[3,2-*h*]isoquinolin-3-ylideneaminoxy]-4-hydroxy-butyric acid) (~~Compound A or B~~) (Step 11); ~~followed by recovery of the desired end product.~~

2. (original) The method of claim 1, which method further comprises the step of

(a) reacting enantiopure (*S*) or (*R*) α -hydroxy- γ -butyrolactone with *N,N*-diBoc-hydroxylamine to give enantiopure (*S*) or (*R*) α -*N,N*-diBoc-aminoxy- γ -butyrolactone (Step 8a); followed by steps (i) to (iii) of claim 1.

3. (currently amended) The method of claim 1, which method further comprises the step of

(b) subjecting *N,N*-diBoc-*O*-benzylhydroxylamine to hydrogenation to give *N,N*-diBoc-hydroxylamine (Step 7);

followed by step (a) reacting enantiopure (*S*) or (*R*) α -hydroxy- γ -butyrolactone with *N,N*-diBoc-hydroxylamine to give enantiopure (*S*) or (*R*) α -*N,N*-diBoc-aminoxy- γ -butyrolactone (Step 8a); and

followed by steps (i) to (iii) of claim 1.

4. (currently amended) The method of claim 1, which method further comprises the step of

(c) converting *O*-benzylhydroxylamine into *N,N*-diBoc-*O*-benzylhydroxylamine using Boc₂O (Step 6);

followed by step (b) subjecting *N,N*-diBoc-*O*-benzylhydroxylamine to hydrogenation to give *N,N*-diBoc-hydroxylamine (Step 7);

followed by step (a) reacting enantiopure (*S*) or (*R*) α -hydroxy- γ -butyrolactone with *N,N*-diBoc-hydroxylamine to give enantiopure (*S*) or (*R*) α -*N,N*-diBoc-aminoxy- γ -butyrolactone (Step 8a); and

followed by steps (i) to (iii) of claim 1.

5. (currently amended) The method of claim 1, which method further comprises the step of

(d) reacting enantiopure (*S*) or (*R*) α -hydroxy- γ -butyrolactone with tosyl chloride to give enantiopure (*S*) or (*R*) α -tosyloxy- γ -butyrolactone (Step 5);

followed by step (c) converting *O*-benzylhydroxylamine into *N,N*-diBoc-*O*-benzylhydroxylamine using Boc₂O (Step 6);

followed by step (b) subjecting *N,N*-diBoc-*O*-benzylhydroxylamine to hydrogenation to give *N,N*-diBoc-hydroxylamine (Step 7);

followed by step (a) reacting enantiopure (*S*) or (*R*) α -hydroxy- γ -butyrolactone with *N,N*-diBoc-hydroxylamine to give enantiopure (*S*) or (*R*) α -*N,N*-diBoc-aminoxy- γ -butyrolactone (Step 8a); and

followed by steps (i) to (iii) of claim 1.

6. (currently amended) The method of claim 1, wherein the 8-amino-1,2,3,4-tetrahydro-isoquinoline (~~Compound 9~~) derivative of step (i) is 4-(8-amino-2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-*N,N*-dimethyl-benzenesulfonamide (to obtain *N*-[5-(4-dimethylsulfamoyl-phenyl)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-yl]-2-hydroxyimino-acetamide); and

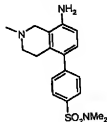
the 2,3-dioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline (~~Compound 11~~) derivative of step (iii) is *N,N*-dimethyl-4-(8-methyl-2,3-dioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinolin-5-yl)-benzenesulfonamide;

giving enantiopure (R)- or (S)-2-[5-(4-dimethylsulfamoyl-phenyl)-8-methyl-2-oxo-1,2,6,7,8,9-hexahydro-pyrrolo[3,2-*h*]isoquinolin-3-ylideneaminoxy]-4-hydroxy-butyric acid as the end product (~~Compound A or B~~).

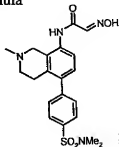
7. – 11. (cancelled).

12. (new) A method of preparing the chiral (\pm) isomers of indole-2,3-dione-3-oxime derivatives in accordance with claim 1, which method comprises the sequential steps of:

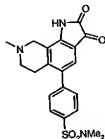
(i) reacting an 8-amino-1,2,3,4-tetrahydro-isoquinoline of the formula



with chloral hydrate and hydroxylamine hydrochloride to give an *N*-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-2-hydroxyimino-acetamide of the formula



(ii) adding sulphuric acid to the *N*-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-2-hydroxyiminoacetamide obtained in step (i) to provide a 2,3-dioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline of the formula

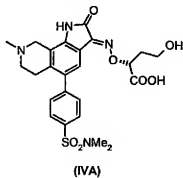


; and

(iii) reacting the 2,3-dioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline obtained in step (ii) with chiral (enantiopure (*R*) or (*S*)) α -*N,N*-diBoc-aminoxy- γ -butyrolactone of the formula



to obtain the desired chiral enantiopure (*R*)- or (*S*)-2-[2-oxo-1,2,6,7,8,9-hexahydro-pyrrolo[3,2-*h*]isoquinolin-3-ylideneaminoxy]-4-hydroxy-butyric acid of the formula (IVA) or (IVB)



or

